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The Role of GABA-Mediated Inhibition in the Rat Ventral Posterior Medial Thalamus. I. Assessment of Receptive Field Changes Following Thalamic Reticular Nucleus Lesions

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SUMMARY AND CONCLUSIONS

1. Changes in the receptive field (RF) properties of thalamic VPM neurons were assessed quantitatively using single-unit recording techniques following a selective excitotoxic lesion of the ipsilateral thalamic reticular nucleus (TRN). The response profiles to controlled deflections of the contralateral vibrissae were obtained from 97 VPM neurons in normal and 102 VPM neurons in TRN-lesioned animals.

2. Histological signs of TRN lesions were detectable in Nissl-stained sections as early as 20 h after the release of kainic acid into TRN.

3. The average RF size of VPM neurons in normal animals was 2.39 ± 0.18 whiskers (mean ± SE). Immediately after the lesion of TRN, the average RF size in VPM was enlarged significantly and remained expanded for as long as 1 mo after the destruction of TRN (7.64 ± 0.47 whiskers, $P < 0.001$).

4. Subsequent lesions of trigeminal subnucleus interpolaris (SpVi) in TRN-lesioned animals produced a marked reduction in the RF size of VPM neurons. The average VPM RF size for TRN/SpVi lesioned animals was 2.14 ± 0.64 whiskers.

5. The loss of inhibition from TRN increased the average response probability and magnitude to the center RF whisker by 38 and 34%, respectively. The response probability and magnitude of the surround RF whiskers increased by 64 and 69%, respectively. The average response latencies to the center and surround RF whiskers were significantly longer after the lesion of TRN; subsequent lesions of SpVi in TRN-lesioned cases reduced the average response latencies of VPM neurons to those seen in normal animals.

6. The RF of VPM neurons in both normal and TRN lesioned cases displayed a strong anterior-posterior ("row") preference. Immediately adjacent anterior-posterior whiskers were twice as likely to elicit a response in VPM than immediately adjacent dorsal-ventral whiskers.

7. VPM units were tested for a preferential response to whisker movement in one of four directions (up, down, backward, and forward). The majority of the neurons in both normal and TRN-lesioned cases showed direction-selective responses, mostly in the up direction. Thus γ-aminobutyric acid (GABA)-mediated inhibition in rat VPM does not appear to be responsible for direction selectivity of VPM neurons.

8. Virtually all neurons in rat VPM after TRN lesions displayed responses that were sustained for the duration of the stimulus (25.5% in normal vs. 88.2% in TRN-lesioned cases). VPM units showing sustained (tonic) responses maintained a high rate of spontaneous activity and, on average, responded to 2–3 times more whiskers than phasically responding units.

9. The results show that the destruction of TRN increases the RF size in the ipsilateral VPM by an average of 3.2-fold. Our data indicate that this increase in the RF size seen after the loss of TRN influence is dependent upon the presence of SpVi. The average number of whiskers that evoked responses in VPM neurons after the destruction of SpVi in TRN-lesioned cases (i.e., whisker-related input mediated by trigeminal subnucleus principalis only) was nearly identical to that of normal animals (2.67 ± 0.31 in normal and 2.14 ± 0.64 in TRN/SpVi-lesioned cases).

10. We conclude from these results that the role of GABA-mediated inhibition in the rat thalamic VPM nucleus is to regulate the number of whiskers that will elicit a response in VPM and to alter the response characteristics by selectively regulating the influence of trigeminal subnuclei interpolaris and principalis on a given VPM neuron.

INTRODUCTION

Since its first description by Cajal (1911), the thalamic reticular nucleus (TRN) has been recognized as being in a key position to influence the transmission of sensory information through specific sensory nuclei in the thalamus. TRN is a thin sheet of purely GABAergic neurons (Houser et al. 1980; Yen et al. 1985) covering much of the lateral surface of the dorsal thalamus. The Golgi studies of Cajal, and later Scheibel and Scheibel (1966), were the first to suggest the intimate relationship between the reticular nucleus and dorsal thalamus. Recent studies using degeneration, autoradiography, or horseradish peroxidase-tracing techniques (Jones 1975; Minderhoud 1971) support the conclusion that the projection of the reticular nucleus is exclusive to the ipsilateral thalamus. Further, Jones (1975) has reported anatomic evidence that the reticular nucleus is subdivided into discrete zones that receive input from collateral branches of specific thalamocortical relay neurons. The axons of reticular neurons project back to the same nucleus of the thalamus, which provides the collateral input, thus completing a precise inhibitory feedback loop (Frigyesi 1972; Harris 1987; Ohara and Lieberman 1985; Peschanski et al. 1983; Schlag and Waszak 1971; Shosaku 1986; Sugitani 1979; Tsumoto and Nakamura 1974). The thalamic reticular feedback circuitry has been implicated in several functions, e.g., varying the efficacy of sensory input (Ahlsen et al. 1985), the genesis of thalamic spindles (Steriade et al. 1987), and in gating selective attention (Yingling and Skinner 1976). Despite clear descriptions of its anatomic and physiological organization, the functional effect of TRN in regulating the transmission of sensory information through the thalamus remains far from complete.

The importance of the reticular nucleus in rats is accentuated by recent findings (Barbaresi et al. 1986; Harris and Hendrickson 1987) that GABAergic inhibition in rat thala-

mic ventral posterior medial (VPM) nucleus arises almost exclusively from the ipsilateral TRN. In view of the recent study by Rhoades et al. (1987) demonstrating that the receptive field (RF) of individual neurons in VPM can be enlarged by selectively removing one of the two trigeminal nuclei relaying vibrissa-evoked input, trigeminal subnucleus principalis (PrV), we particularly were interested in ascertaining whether inhibition arising from TRN is capable of regulating the size of the RF for VPM neurons.

Our aims in the present and accompanying studies were to assess the effect of TRN lesions on the RF of thalamic VPM neurons using quantitative RF-measurement techniques and to identify the contribution of γ-aminobuturic acid-A and -B ($GABA_A$, $GABA_B$)-receptor-mediated inhibition in determining the response properties of VPM neurons to controlled sensory stimuli.

A preliminary account of this work has appeared as an abstract (Lee et al. 1990).

METHODS

Preparation and lesioning

The data in these experiments were obtained from 28 adult Long-Evans rats of either sex weighing between 250 and 350 g (Charles River Laboratory). Kainic acid (KA)-induced, excitotoxic lesions of TRN were made under sodium pentobarbital anesthesia (60 mg/kg, ip). Using stereotaxic coordinates derived from the atlas of Paxinos and Watson (1982), ~50 nl of 2-mM KA (in dH_2O) were injected at three different depths in three penetrations (9×50 nl at AP −2.4, −2.7, −3.3 mm; ML 4.1 mm; D 4.5, 5.0, 5.5 mm from bregma). The delivery system used was a glass micropipette, beveled to an outer tip diameter of ~40 μm, which was connected to an electronically gated pressure regulator (Neurophore, Medical Systems). Brief pulses (100–200 ms) of pressure ranging from 20 to 40 psi ejected predictable volumes of KA. The total amount delivered in vivo was measured by determining changes in position of the meniscus formed by the KA solution in a micropipette with a 0.68-mm ID (6020 capillary; AM Systems). With the aid of an operating microscope fitted with an eyepiece reticle, the amount of KA injected could be calibrated to volumes as small as 10 nl. The injection pipette was placed usually 0.5 mm lateral to TRN to minimize the diffusion of the excitotoxin into VPM. The survival times after the lesions were varied depending on the specific experiment. The extent of the lesions was verified in all cases by carefully examining Nissl-stained sections for any remaining neurons.

In some experiments, TRN was lesioned during the recording experiment to compare the changes in RF size before and immediately after the lesioning procedure. In these cases, the recording electrode was left in place in VPM while the injection pipette was placed lateral to TRN. The presence of the recording electrode allowed us to monitor the time course of the KA-induced hyperexcitability in VPM.

Trigeminal subnucleus interpolaris (SpVi) was lesioned using the methods of Rhoades et al. (1987). In brief, three 0.3-μl KA (2 mg/ml in dH_2O) injections were made into SpVi at three distinct coordinates [(in mm) AP −12.0, −12.5, −13.0; ML −2.7; D 7.0]. Unitary VPM recordings from SpVi-lesioned cases were followed throughout the lesioning procedure, and the RF compared before and after the removal SpVi input.

Electrophysiological recording

For recording experiments, the animals were anesthetized with an intraperitoneal injection of urethane (1.5 g/kg body wt; Sigma) and maintained at a constant anesthetic depth with supplemental doses by monitoring the electrocorticogram (ECoG). The core body temperature was maintained at 37–37.5°C by a thermostatically controlled heating pad. A local anesthetic (bupivacaine hydrochloride or Lidocaine) was applied to all surgical fields and other traumatic points. A small craniotomy (~1 mm^2) was made directly above the left VPM (AP −3 mm, ML 3 mm from bregma), and the dura carefully reflected. Three steps were taken routinely to reduce the cardiovascular pulsation of cerebral hemispheres and the respiratory-induced movements of the brain: *1*) the cerebral spinal fluid (CSF) was drained by making an opening in the cisterna magna, *2*) a 4% solution of agar was allowed to harden over the entire surgical field before a small opening was carved out to facilitate electrode penetration, and *3*) the dura was left in place as much as possible. The "well" fashioned from the agar was kept filled with warmed physiological saline or artificial CSF.

Single-unit responses were recorded extracellularly with carbon fiber microelectrodes (0.5–2 MΩ at 1 KHz) (Armstrong-James and Millar 1979) and amplified using conventional techniques. Single units were discriminated by displaying the entire somatic action potential on a digital oscilloscope (Nicolet 310), and an amplitude-time discriminator (BAK Instruments) was used as an event-detector to isolate the desired waveform. Somatic spikes were distinguishable from those generated by axons by their initial negativity and longer spike duration (Hubel 1960; Simons and Carvell 1989). Precise vertical advancement of the recording electrode was facilitated by a stepping microdrive (Kopf Instruments) equipped with a digital counter. Our previous experience and reports from other laboratories (Ito 1988; Saporta and Kruger 1977; Sugitani 1979; Waite 1973a) indicated that the vibrissa-evoked responses in VPM were restricted to the dorsolateral portion of VPM, and all penetrations thus were confined to that region.

Because the location of the thalamic neuron studied was often critical in the interpretation, the recording sites and/or end of the electrode tracks were marked by passing current (10 μA for 10 s, tip negative). At termination of the experiment, animals were anesthetized deeply with sodium pentobarbital and perfused transcardially with 200 ml of phosphate buffered saline followed by 4% paraformaldehyde solution. Coronal sections 75-μm thick were cut on the sliding microtome, and alternate sections reacted for cytochrome oxidase (CO) according to the method of Wong-Riley (1979). The remaining sections were stained with 2% cresyl violet. The electrolytic microlesions marking the recording sites were readily discernible on the CO-reacted sections, which appeared as pale, circular regions 50–120 μm in diameter. The electrode tracks were reconstructed using the micrometer readings and the electrolytic marks in order to confirm that the units studied were located within VPM.

Monitoring of anesthetic state

The importance of precisely monitoring the anesthetic state of the animal while recording unitary activity has been emphasized in our previous reports (Friedberg et al. 1991; Lee and Ebner 1992). In brief, the depth of anesthesia was categorized using the terminology of Guedel (1920). The characteristic signs for each stage were determined using the ECoG and a number of other physiological indicators, which include pupillary size, respiratory rate, electrocardiogram, corneal reflex, and pinch-withdrawal reflex. For the placement of the ECoG electrode, a pin hole was drilled through the skull over the right parietal cortex [approximately (in mm) AP 2.0, ML 2.0 from bregma], and a low-impedance (<500 KΩ at 100 Hz) tungsten electrode was inserted 1–1.5 mm beneath the cortex surface. The signals were bandpass filtered between 0.1 and 50 Hz and displayed as a power spectrum in a condensed spectral array format (Modular Instruments). The dominant ECoG frequency and the anesthetic stage, i.e., III-2 (5–7 Hz), III-3 (3–4 Hz), and III-4 (1–2 Hz), were noted for each RF

measurement. All RF measurements reported in this study were assessed at a single anesthetic depth, which we have determined as III-3 (Friedberg et al. 1991). Physiological indicators at III-3 include respiratory rate at 88–104 per min, heart rate at 232–350 per min, and the presence of corneal and eyelid reflexes, but no withdrawal to pinch or movement of the vibrissae.

Stimulus control and data acquisition

Discrete, controlled movements of individual whiskers were carried out using a piezoelectric mechanical stimulator (Simons 1983). A metal probe attached to the piezoelectric stimulator deflected the whisker ~300 μm in one of four directions: up, down, backward, or forward. The whiskers were trimmed to a length of ~10 mm from the face and the placement of the stimulator in relation to the whisker was kept constant at ~5 mm from the base of the whisker. The duration and frequency of the stimuli were maintained at 10 ms and 1 Hz, respectively, unless stated otherwise. The stimulator and data acquisition were both controlled by a computer interfaced through a series of high-speed clocks and memory modules (IBM-AT and Modular Instruments). The responses to deflections of the whiskers were displayed "on-line" during the course of the experiment as a peri-stimulus time histogram (PSTH). A typical sampling time consisted of 300 ms of prestimulus activity and 200 ms sampling of poststimulus response time. The number of trials per stimulation protocol was kept constant throughout this study at 30 stimulus presentations. The 9 s of prestimulus activity (300 ms per trial × 30 trials) were used to calculate the spontaneous activity for each neuron.

The center receptive field (CRF) was defined operationally as the vibrissa eliciting the highest response probability in a VPM neuron; all other effective whiskers for that neuron were classified as the surround receptive field (SRF). The SRF responses presented in this study represent the average response values of all SRF whiskers for a given VPM neuron.

All units isolated for this study were tested for sustained responsiveness. Responses in VPM units were classified as being tonically or phasically responding using the following criteria. After determining the RF map of a VPM neuron, the CRF whisker was used to test for tonic responsiveness using a 50-ms deflection of the whisker. If the first and second halves of the response period (the first 25 ms after stimulus onset) gave responses that were significantly higher than the prestimulus activity, the unit was classified as responding tonically. If either the first or second test periods failed to produce responses that were above background or if the second half of the response was <0.5 of the first half, the unit was classified as responding phasically. Typically, a tonically responding unit responded continually for the duration of the 50-ms deflection of a whisker.

Data analysis

For a cell discharge to qualify as a stimulus-evoked response during the response time period (2–50 ms after the onset of the stimulus), a distinct mode with at least three spikes had to accumulate in the PSTH at a single latency after 30 stimulus presentations. The rationale for this criteria was based on the statistical improbability of three random events occurring at a given time bin. Each unit accepted as being responsive had a statistically significant increase in the rate of firing during the response time when compared with an equal duration of the prestimulus activity. These standards are similar to those reported previously in studies of the somatosensory cortex of rats (Armstrong-James and Fox 1987).

"Off-line" analysis of the data consisted of converting spike times to one of the following formats: response probability, response magnitude, response latency, and rate of spontaneous activity. *Response probability* was used as a measure of how well a unit followed a 1-Hz stimulation of a whisker in its RF. The maximum value of 1.0 indicated that the unit responded with at least one spike to each stimulus presentation. *Response magnitude* measured the average number of spikes per stimulus. This was computed as follows: Resp Mag = $[\Sigma(Spikes_R) - \Sigma(Spikes_{SA})]/NStim$ where $Spikes_R$ is total number of spikes during the response time, $Spikes_{SA}$ is total number of spikes during an equal length of the prestimulus sampling period, and *NStim* is the number of stimulus presentations. The *response latency* was determined as the mode of the latency histogram that plotted the frequency of the first spike during the response period. *Spontaneous activity* was computed as the average spike frequency during the prestimulus time in Hz.

For VPM units that were tested for direction selectivity in one of four directions, a vibrissa-responding unit was categorized as being "well tuned" if it displayed a null response to a particular direction. A neuron was classified as being "poorly tuned" if it responded to all four directions, but showed a statistically significant preference in one direction. All other units were classified as "not tuned." Typically, the difference in response probability between the best and worst directions for a well-tuned unit was ≥0.7.

Statistical significance was determined using a Student's *t*-test at a confidence level of $P < 0.05$. Changes in direction selectivity were tested using a χ^2 test.

RESULTS

The receptive field characteristics of 102 VPM neurons from 15 animals are reported after excitotoxic lesions of the TRN. In seven of these cases, a multiwhisker VPM unit was "held" while the contralateral SpVi was lesioned ($n = 7$ neurons). The RF profiles of 97 VPM units were obtained under identical conditions from nine unlesioned (normal) animals for comparison. The short-term changes in the receptive field properties of VPM neurons after TRN lesions (4 cases) were recorded from 33 units. The number of units isolated per experiment was kept between 9 and 15 to ensure that the electrode penetrations were made far enough apart for a representative sampling of VPM while not interfering with the identification of the lesion sites.

An important and consistent finding of the TRN-lesioning procedure was that each case injected with KA showed a nearly complete destruction of TRN regardless of the precise amount and location of the delivery. Similar observations regarding the acute sensitivity of TRN to KA insults have been reported previously (Peschanski et al. 1983; Peterson and Moore 1980; Steriade et al. 1987). Analysis of the Nissl-stained sections showed that the death of TRN neurons could be detected as early as 20 h after the release of KA (Fig. 1).

The release of KA near TRN was followed by a predictable sequence of events as detected by the recording electrode positioned in VPM during the injection procedure. The spontaneous neuronal activity in VPM decreased markedly within 1–2 min after the release of excitotoxin into TRN. This transient event was assumed to reflect an increased inhibitory influence that resulted from a sudden increase in the activity of TRN neurons by the presence of the excitotoxin. This initial depression in VPM activity lasting 10–15 min was consistent with the finding by Mushiake et al. (1984) who proposed that the presence of KA in TRN increases the inhibitory drive on VPM neurons by directly activating TRN neurons. The marked suppression of neuronal activity in VPM was inevitably followed by a three- to fivefold increase in the spontaneous firing of VPM neurons,

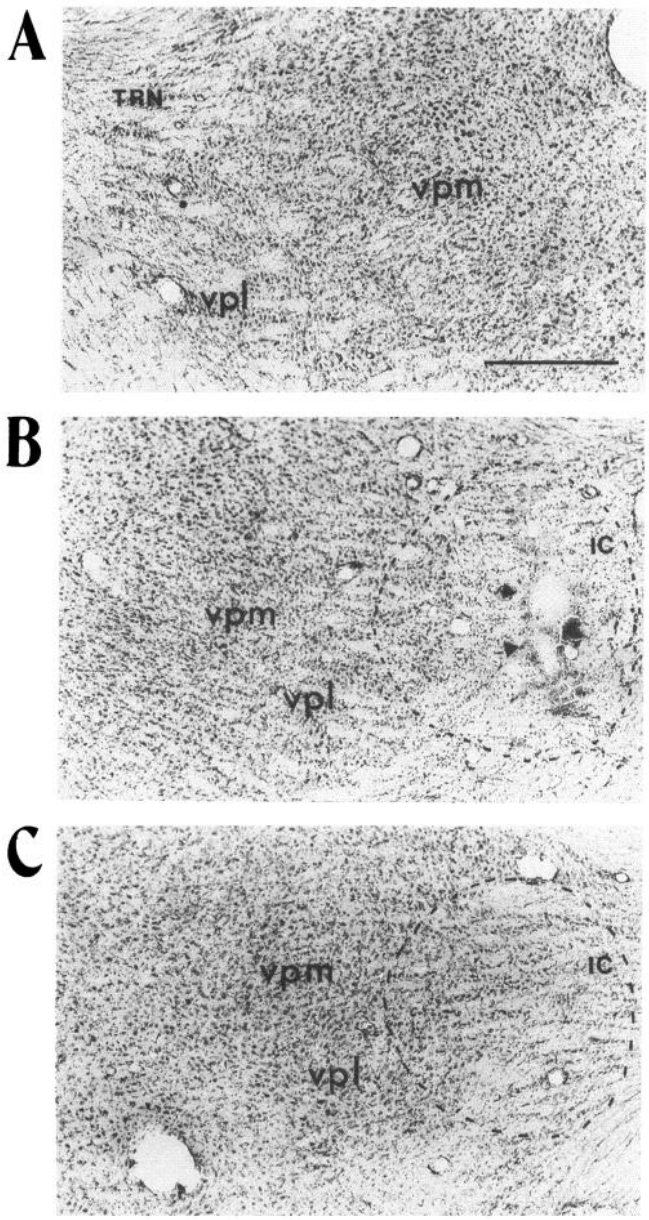

FIG. 1. Coronal sections stained with cresyl violet for normal animals (*A*) and after 1 d (*B*) and 1 wk (*C*) after kainic acid (KA) lesions of the thalamic reticular nucleus (TRN). The injection electrode was placed ~0.3 mm lateral to TRN in the internal capsule (IC). A complete loss of neurons was discernible in the TRN region within 20 h after KA injections. The extent of the lesions is outlined by the dashed lines. Calibration bar = 0.5 mm.

the firing lasted from 2 to 4 h. The rate of hyperactivity was similar to cases in which KA was injected directly into VPM and thus was presumed to be caused by the diffusion of KA through much of the dorsal thalamus. The RF size for VPM units was reassessed after the neuronal activity had returned to preinjection levels.

In a few cases in which the volume of KA inadvertently exceeded 100 nl per injection (5 out of 24), the increased firing of VPM neurons persisted for as long as 10–12 h. The evoked responses in such cases failed to return to normal as the spike amplitude consistently remained <100 μV. In addition, the evoked responses lacked a definitive RF and were unable to follow our standard 1-Hz stimuli. The subsequent histological analysis at the termination of the experiment always revealed that a major portion of VPM contained shrunken cells that were presumably degenerating. The five such cases were excluded from this study.

RF properties of normal VPM neurons

Table 1 lists the population averages and distributions for the response of VPM neurons in normal animals to the stimulation of vibrissae in their RF and the changes seen following a selective lesion of TRN. On average, normal VPM neurons responded vigorously to the movement of one to three adjacent whiskers. The response profile for a representative VPM neuron can be seen in Fig. 2.

The response profile of a given VPM unit generally consisted of a single CRF whisker and one to two SRF whiskers. All thalamic units tested under our recording conditions had a clear CRF whisker that differed from SRF by >10% in response probability. No attempt was made to correlate the CRF whisker with its appropriate "barreloid" location. The response probability for the CRF whisker ranged from 0.6 to 1.0. The SRF whiskers gave responses that were more variable, but the average difference between the CRF and SRF response probabilities was never >0.4. These results are consistent with recent RF studies in normal rat VPM under moderate urethane anesthesia (Armstrong-James et al. 1991; Sugitani et al. 1990).

RF properties in VPM after TRN lesions

The time course of the RF changes after a selective lesion of TRN was assessed in one of two ways. One method was to lesion TRN during the course of a recording experiment while the recording electrode was left positioned in VPM. Figure 3 depicts the results of two experiments carried out using this strategy. The RF of all VPM neurons mapped before the TRN lesion ranged from one to three vibrissae, but never exceeded three whiskers. In contrast, the RFs for all neurons assessed following the excitotoxic lesion of TRN were dramatically larger, displaying RFs that ranged from 4 to 15 whiskers. Thus the effect of TRN lesions was a

TABLE 1. *Average response values and proportions for VPM units*

	Normal	TRN Lesion	TRN/SpVi Lesion
n	97	102	7
RF Size	2.67 ± 0.31	8.81 ± 0.98*	2.14 ± 0.64†
CRF whiskers[1]	1.0	1.0	1.0
SRF whiskers	1.67 ± 0.31	7.81 ± 0.98*	1.33 ± 0.64†
Probability	0.40 ± 0.03	0.60 ± 0.06*	0.42 ± 0.07†
CRF whiskers	0.53 ± 0.03	0.73 ± 0.07*	0.67 ± 0.06*
SRF whiskers	0.28 ± 0.03	0.46 ± 0.06*	0.26 ± 0.07†
Magnitude	0.57 ± 0.06	0.82 ± 0.11*	0.72 ± 0.11*
CRF whiskers	0.74 ± 0.07	0.99 ± 0.13*	1.10 ± 0.16*
SRF whiskers	0.39 ± 0.05	0.66 ± 0.09*	0.47 ± 0.08
Latency	6.81 ± 0.48	9.80 ± 1.25*	6.73 ± 1.01†
CRF whiskers	5.90 ± 0.35	5.70 ± 0.40	5.67 ± 1.38
SRF whiskers	7.72 ± 0.62	11.21 ± 1.34*	9.13 ± 0.9
Tonic %	25.5 ± 6.2%	88.2 ± 9.8%*	79.0%*
Direction Selective %	86.4 ± 4.6%	82.4 ± 3.5%	—

Values expressed as means ± SE. [1] by definition, the RF of CRF whisker is 1 (see METHODS); * $P < 0.01$ when compared with normal aniamls; † $P < 0.01$ when compared with TRN-lesioned animals.

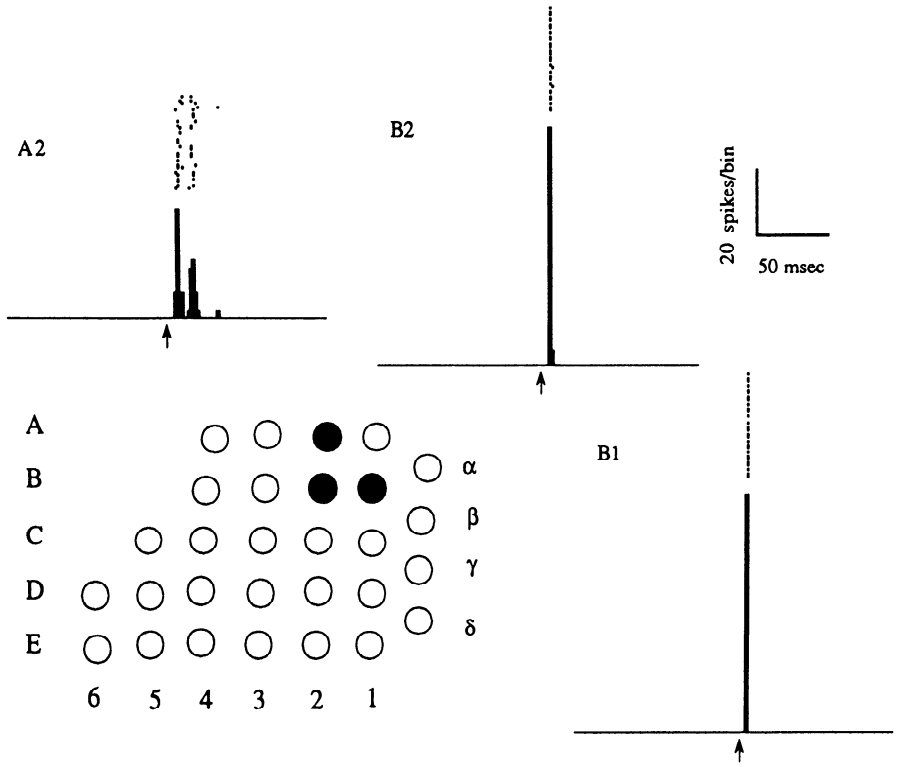

FIG. 2. Peri-stimulus time histogram (PSTH) response profiles for the 3 whiskers (A2, B1, B2) constituting the receptive field of a representative ventral posterior medial (VPM) neuron from a normal animal (number of stimuli for each histogram, 30). Location is shown of the 3 whiskers on the whisker pad (*inset*). The onset of the 10-ms stimulus is indicated by the arrows. Each vibrissa in the receptive field (RF) of this VPM neuron elicited a high-probability response (range, 0.7–1.0).

two- to fivefold increase in the average RF size seen in VPM neurons within 2 h after the TRN lesions.

The other method employed for assessing the time course of the RF enlargement was to vary the survival time from 1 day to 1 mo after the TRN lesion. The average RF for 1-day, 2-day, 3-day, and 1-mo survival cases can be seen in Fig. 4. The larger RF (average = 7.41 whiskers) seen in VPM after 1-day survival was virtually identical to the ones measured in longer-term survival cases (2 day to 1 mo, Fig. 4).

Previous studies (Friedberg et al. 1989, 1991; Rhoades et al. 1987) have demonstrated that the enlargement of RF size in VPM can be mediated by the SpVi. In the present study, the RF enlargement induced by the TRN lesion was followed by a KA lesion of SpVi. In each of these cases, one multiwhisker VPM unit was "held" for ~2 h while the SpVi input was removed (n = 1 unit/case in 7 animals). The RFs seen in VPM immediately after such SpVi lesions were indistinguishable from those seen in unlesioned animals (Fig. 4).

The PSTH profiles for a representative VPM neuron 3 day after a TRN lesion can be seen in Fig. 5. As in the response profiles for normal VPM neurons, the center-surround RF organization was maintained even in the absence of γ-aminobutyric acid (GABA)-mediated inhibition. Compared with normal VPM units, 98 out of the 102 VPM units (96%) in TRN-lesioned animals (vs. 100% in unlesioned cases) had a clear CRF whisker that was ≥10%

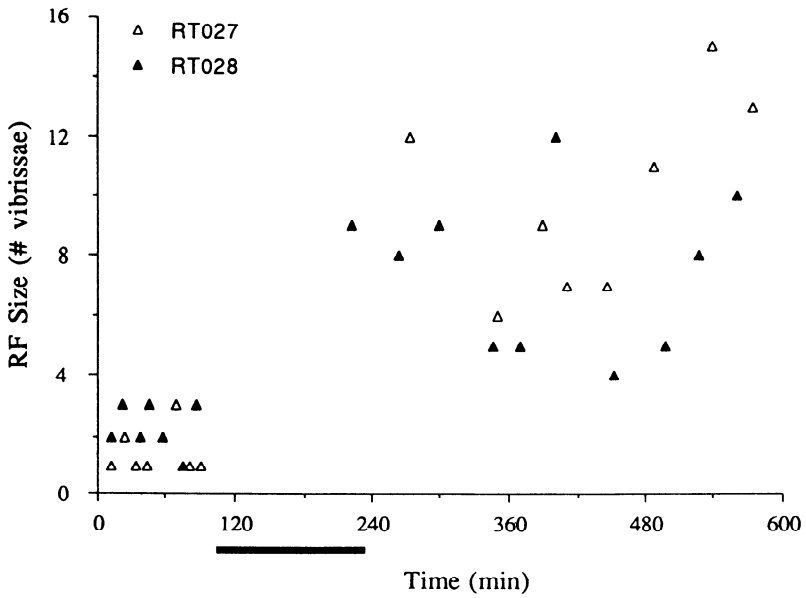

FIG. 3. Changes in the RF size of VPM neurons within 2 h after KA injections into the thalamic reticular nucleus. The data from 2 cases, RT027 and RT028, are plotted as a function of time before and after the KA injection. The *left end* of the black bar indicates the onset of the injection, which lasted ~15 min. The length of the bar indicates the period of increased spontaneous activity of VPM neurons because of diffusion of the excitotoxin into VPM. There was no overlap between the size of VPM RFs before and after destruction of the reticular nucleus; the receptive fields always increased in size to >4 whiskers.

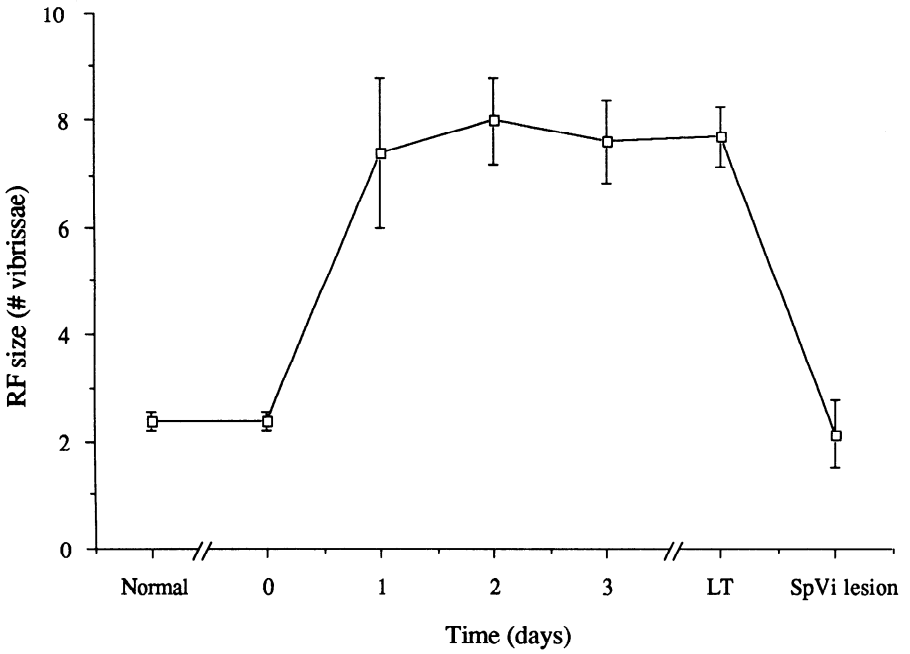

FIG. 4. Average RF size of VPM neurons before (2.39 whiskers, n = 102) and after (7.64 whiskers, n = 97) the destruction of TRN (*Day* 0). The dramatic increase in average RF size persisted throughout the range of survival times tested (1–30 day). Each time point represents the average of >30 VPM units. Subsequent lesions of trigeminal subnucleus interpolaris (SpVi) after determining the RF size at 30 days in TRN-lesioned animals resulted in a marked reduction in the RF size back to prelesion (normal) levels (2.14 whiskers, n = 7 cases). Time points present as means ± SE.

higher in response probability than any SRF whisker. Further, for every VPM unit mapped in normal and TRN-lesioned cases, all whiskers in the SRF were contiguous with no discontinuous jumps in the RF.

In addition to the two- to fivefold increase in the RF size, the most startling feature of evoked responses in VPM in the absence of TRN-mediated inhibition was the increase in the response latency to the SRF whiskers (see Table 1 for

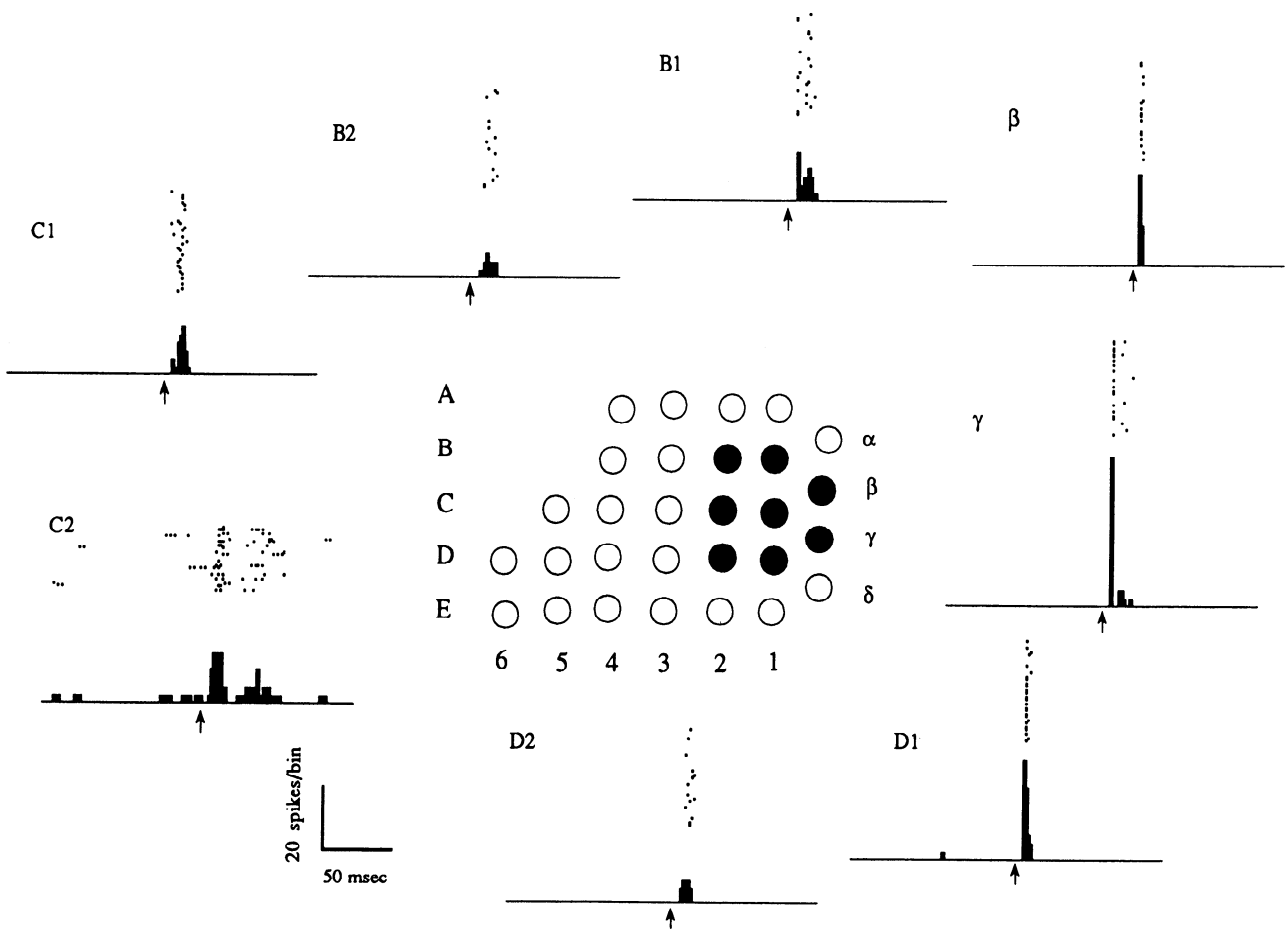

FIG. 5. PSTH response profiles for the 8 whiskers constituting the RF of a representative VPM neuron 3 days after a TRN lesion (number of stimuli for each histogram = 30). Location of the 8 whiskers on the whisker pad is shown (*inset*). Half of the RF (C2, D1, β, γ) elicited a response that was >0.6 in response probability. The onset of the 10-ms stimulus is indicated (→).

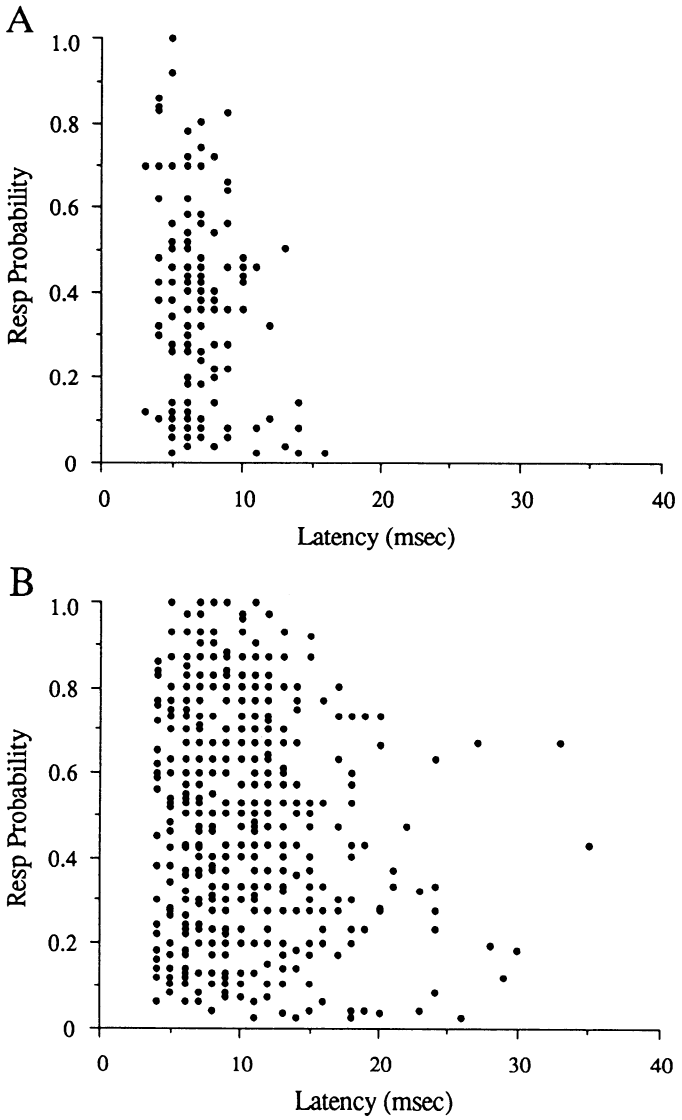

FIG. 6. Plot of response probability vs. latency of all center receptive field (CRF) and surround receptive field (SRF) whiskers for 97 units from normal animals (*A*) and 102 units from TRN-lesioned cases (*B*). Values for CRF whiskers, (○); values for all SRF whiskers, (●). Note the marked increase in the number of whiskers that elicited high-probability responses at a longer latency (>12 ms); a finding that was rarely seen for normal VPM neurons.

comparison). The response probabilities of each whisker that elicited a response, for all VPM neurons included in this study, are depicted in Fig. 6 as a function of response latency. Compared with only 14.5% of the whiskers that gave responses at a latency of ≥10 ms in normal animals, nearly half (49.7%) of the whiskers gave responses at those latencies after the loss of inhibition from TRN. The response latencies of the SRF whiskers in TRN-lesioned cases ranged from as short as 5 ms to as long as 34 ms (11.2 ± 1.3 vs. 7.8 ± 0.6 ms in normal animals, $P < 0.001$). As in the enlargement of the RF, the longer latency responses were mediated through SpVi as its subsequent destruction in TRN-lesioned cases completely abolished all responses >10 ms (9.13 ± 0.9 ms); a finding that is similar to a previous report from our laboratory in which response latencies were measured immediately after disconnecting the SpVi input (Friedberg et al. 1991). A comparison of the average latencies of CRF whiskers only in normal and TRN-lesioned animals failed to show a significant difference (5.9 ± 0.35 vs. 5.7 ± 0.4 ms, respectively).

Thus the increase in the average response latency of VPM units after TRN lesions was because of a marked increase in the number of SRF whiskers that gave responses at significantly longer latencies than the CRF whisker.

Organization of CRF-SRF relationship

To facilitate the comparison of RF organization in normal and TRN-lesioned cases as a population rather than as individual units, the RF of each unit was "aligned" by centering the CRF whisker on a coordinate scheme. Thus for each VPM unit, the CRF whisker was given the coordinate (0,0) and placed on a rectangular grid with (0,0) as the center. The response probabilities evoked by each whisker in the RF were averaged and plotted in three dimensions with response probability on the *Z*-axis (Fig. 7). To remove any asymmetry in the RF that may be imposed artificially by the CRF whisker on the edge of the vibrissa pad, units with CRF whiskers on the *A* or *E* rows or α, β, γ, or δ CRF whiskers were excluded from the population maps. The population probability maps for 54 (out of 97) normal units and 67 (out of 102) TRN-lesioned units can be seen in Fig. 7. The most striking feature of these population maps is that the center-surround relationships was maintained after the loss of inhibition from TRN. Each plot shows a clear CRF that has a significantly greater response probability than any adjacent whisker.

The average RF size as a function of axis for units included in the alignment procedure is summarized in Fig. 8. The dorsal-ventral axis represents the arcs and anterior-posterior axis, the rows. As a population, VPM neurons display a strong row preference under both normal and TRN-lesioned conditions. Thus, on average, nearly 4.5 as many whiskers in a single row activated a given neuron in VPM as did whiskers in a single arc. This anterior-posterior bias was somewhat diminished for the TRN-lesioned population, but the difference remained nearly 2.3-fold.

As a summary, Fig. 9 graphically demonstrates the changes in response properties after the loss of inhibition from TRN. The RF organization of VPM neurons maintains the stronger CRF and the relatively weaker SRF relationship even in the absence of inhibition. After the TRN lesion, there was a concomitant increase in the response probability of both the CRF and SRF whiskers (Fig. 9*A*).

Response dynamics

Approximately 25% of VPM units were categorized as tonically responding units in control animals using our definition of tonic responsiveness (see METHODS). In contrast, almost all units tested after the TRN lesions responded with sustained discharges (88.0%). Units that were tonic or phasic also were compared in terms of their average RF size, rate of spontaneous activity, response probability, and latency (Fig. 10). In general, tonically responding VPM neurons had significantly larger RFs and higher response probabilities in both normal and TRN-lesioned animals than phasically responding cells ($P < 0.01$ level). The spontaneous activities and average response latencies of tonically and phasically responding neurons were not significantly

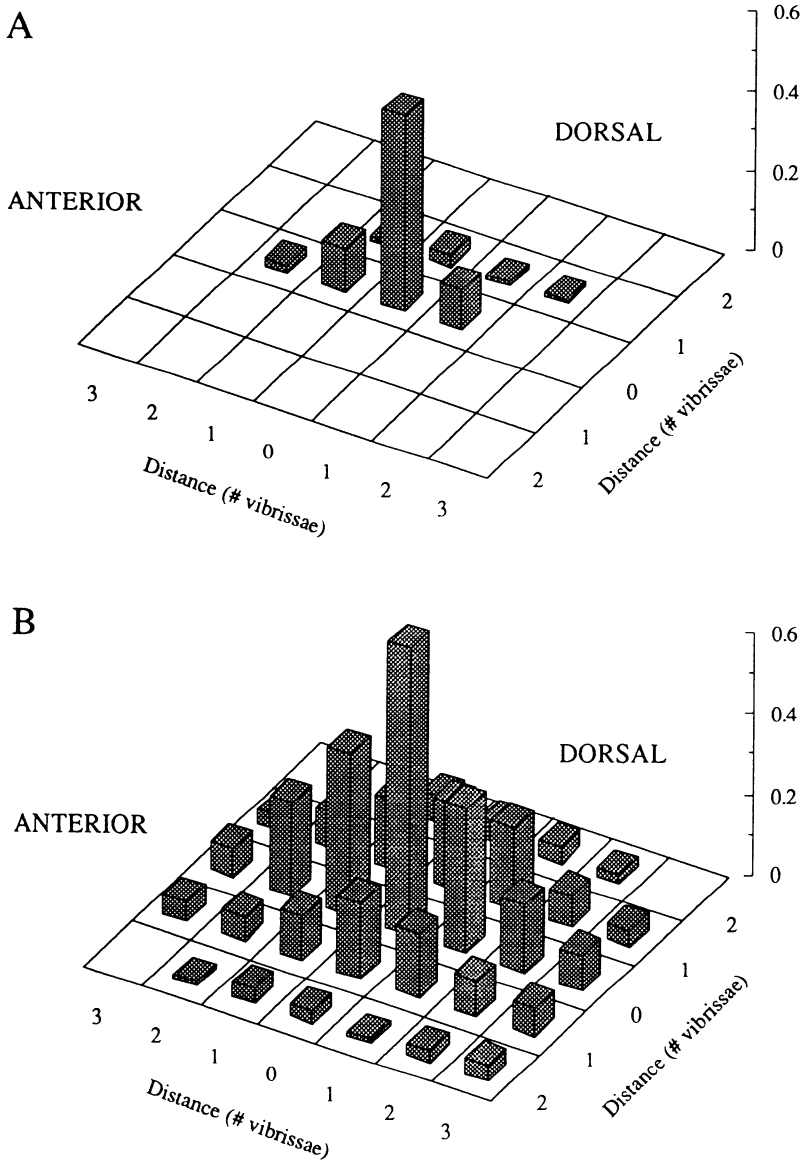

FIG. 7. Comparison of a normalized representation of the average response probability of 54 VPM neurons from normal animals (*A*) and 67 units from TRN-lesioned cases (*B*). The height of the bars represents average response probability. The anterior-posterior axis represents the "rows" and dorsal-ventral axis depicts an "arc." The CRF whisker (0,0) had a clearly higher probability of response than the SRF whiskers under both conditions (see text for methods used to normalize responses).

different in normal animals, but became strikingly so after the loss of TRN ($P < 0.01$). The average spontaneous activity of tonically responding units after the lesion of TRN was nearly 20 times higher than phasically responding ones. The response latency of phasic units was 29% longer than tonically responding neurons after the destruction of TRN; this percentage was highly significant ($P < 0.001$, Fig. 10).

Comparison of tonic and phasic units before and after TRN destruction revealed two important conclusions: for tonically responding units, the only statistically significant change was the increase in the RF size and for phasic units, changes in all four response characteristics were significant at least at the P value of 0.05 (Fig. 10).

Direction selectivity

Forty-two normal and 66 VPM units in TRN-lesioned animals were tested for preferential sensitivity to the stimulation of the CRF whisker in one of four directions—up, down, backward, and forward. Almost all neurons, in both normal and TRN-lesioned cases, displayed signs of direction selectivity (86.4 and 82.4%, respectively; Fig. 11*A*). In both normal and lesioned cases, movements in the up direction were clearly preferred rather than other directions ($P < 0.001$, Fig. 11*B*).

Although the proportion of direction-sensitive units to those that lacked a clear preference remained nearly identical after the TRN lesion ("not tuned" in Fig. 11*A;* 13 vs. 17%, respectively), there appeared to be a slight decrease in the percentage of units that was well tuned, a value that was not statistically significant (Fig. 11*A*, $P > 0.20$, χ^2 test).

Involvement of SpVi in RF enlargement

In seven TRN-lesioned cases, responses of VPM neurons were recorded while the contralateral SpVi was excitoxically lesioned using KA. Using the RF alignment procedure described above (see Fig. 7), the population-probability map for seven TRN/SpVi-lesioned cases is shown in Fig. 12. The population RF profile after the subsequent SpVi lesion appeared remarkably similar to the one constructed for normal VPM neurons (compare with Fig. 7*A*); the average RF size was identical to those of normal units, but the CRF whisker showed a 57% increase in response probability (Fig. 13). The average response latency to all

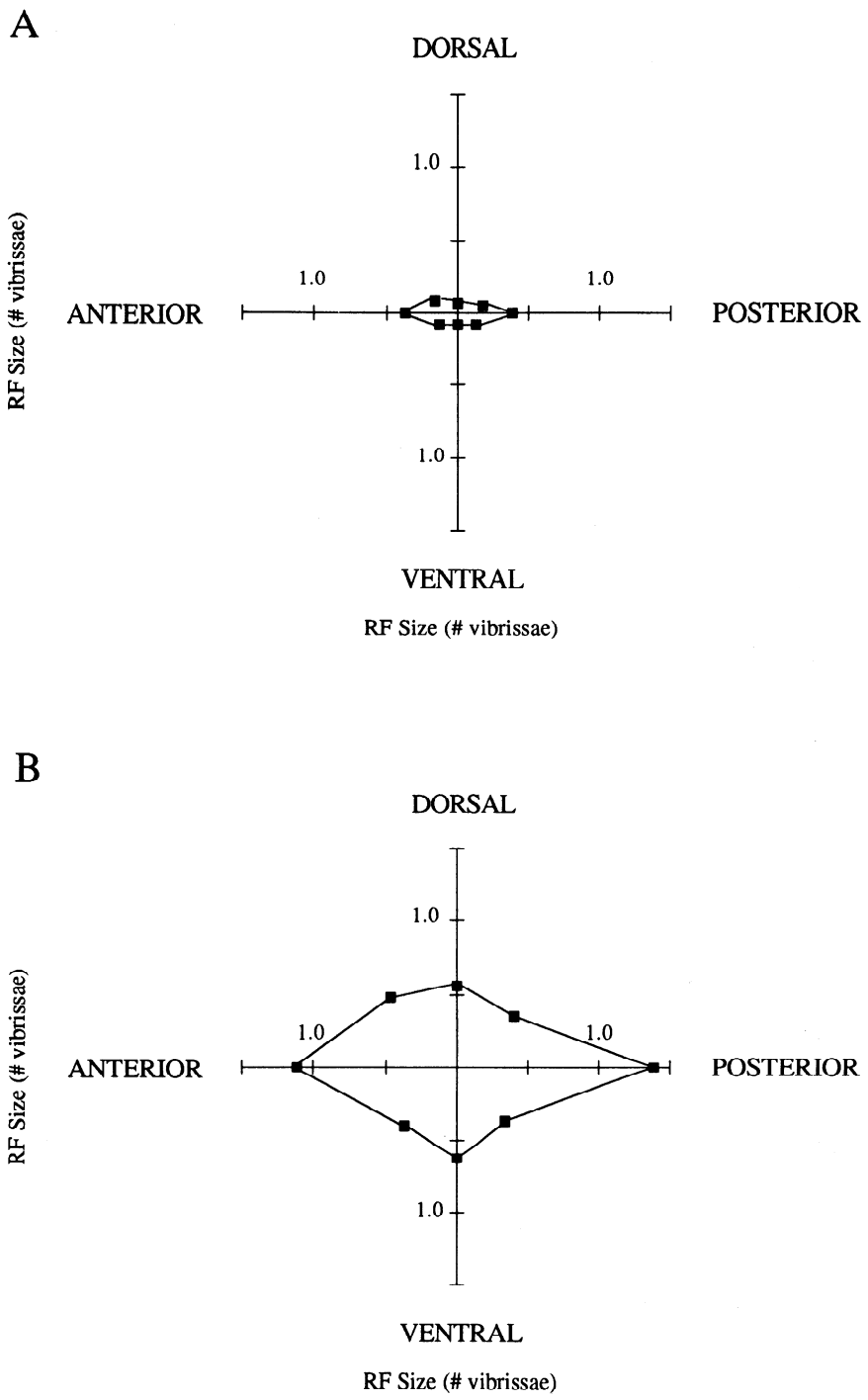

FIG. 8. Polar plots of the average RF size in the dorsal, ventral, anterior, and posterior axes from the CRF whiskers (0,0) in normal (*A*) and TRN-lesioned (*B*) animals. The dorsal-ventral axis constitutes an arc, whereas the anterior-posterior axis represents a row of whiskers. For both normal and TRN-lesioned animals, the shape of the RF in VPM displayed a clear asymmetry in favor of the anterior-posterior axis.

whiskers after the loss of TRN and SpVi was nearly identical to normal animals, yet significantly shorter than in animals with TRN lesions only ($P < 0.01$, Table 1). The proportion of cells showing tonic responses diminished slightly after the subsequent destruction of SpVi, but it was determined not to be statistically significant (Table 1).

The loss of input from SpVi after TRN destruction reduced the RF back to the size seen in VPM neurons of normal animals. However, the response probability and magnitude remained elevated for both the CRF whiskers and the few remaining SRF whiskers. The average latencies of the CRF and SRF whiskers in TRN/SpVi-lesioned cases were nearly identical to the ones seen in normal animals (Table 1).

DISCUSSION

Methodological considerations

The role of GABAergic inhibition in the transmission of vibrissa-evoked information in the thalamic VPM nucleus was assessed by selectively removing the ipsilateral TRN from the trigemino-thalamo-cortical circuit. As with any lesion study, the strength of the results is critically dependent on the effectiveness and selectivity of the lesioning procedure. Some recent studies have reported that TRN neurons are especially sensitive to excitotoxic insults (Peschanski et al. 1983; Peterson and Moore 1980; Steriade et al. 1987), so the primary concern for the present study was to determine that the effect of KA was not directly on

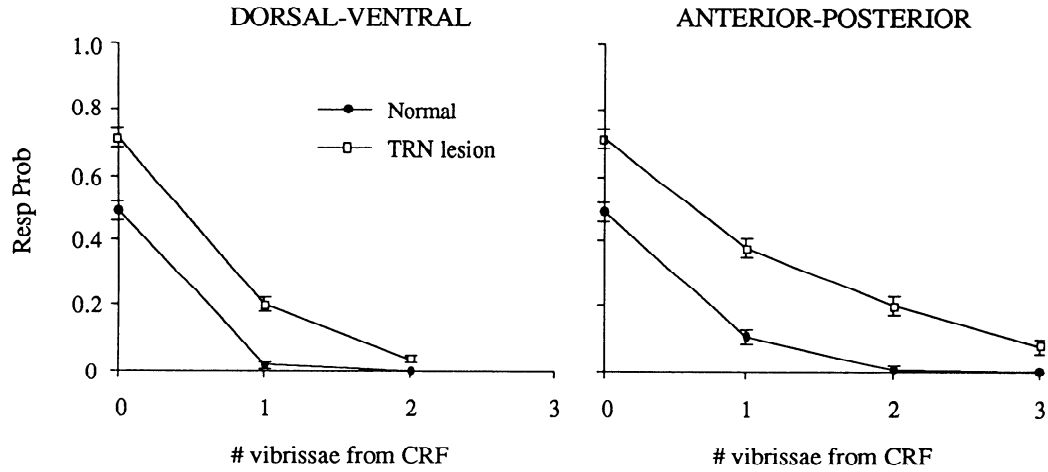

FIG. 9. Plot of average response probability as a function of the number of whiskers from CRF in the dorsal-ventral and anterior-posterior axes. Note that the CRF-SRF relationship remained proportional to normal animals even in the absence of TRN-mediated inhibition. The differences between the lines representing normal and TRN-lesion cases denote the increase in the responsiveness following the loss of inhibition. Plots expressed as means ± SE.

VPM, which lies in close proximity to TRN. In addition, recent reports (Horn and Carey 1987; Walker and McAllister 1986) have suggested that axons of passage can be damaged by KA leading to a retrograde degeneration of thalamic and cortical neurons.

Several lines of evidence demonstrated that we selectively removed the inhibitory influence of TRN using our lesioning paradigm without destroying cells in VPM or thalamocortical and/or corticothalamic fibers. First, the topography of TRN is well established; the area of TRN devoted to processing of somatic sensation is restricted to the anterolateral borders of the ventrobasal nucleus (Harris 1987; Jones 1975; Shosaku et al. 1984). In all cases assessed in this study after the lesioning procedure, no TRN neurons in

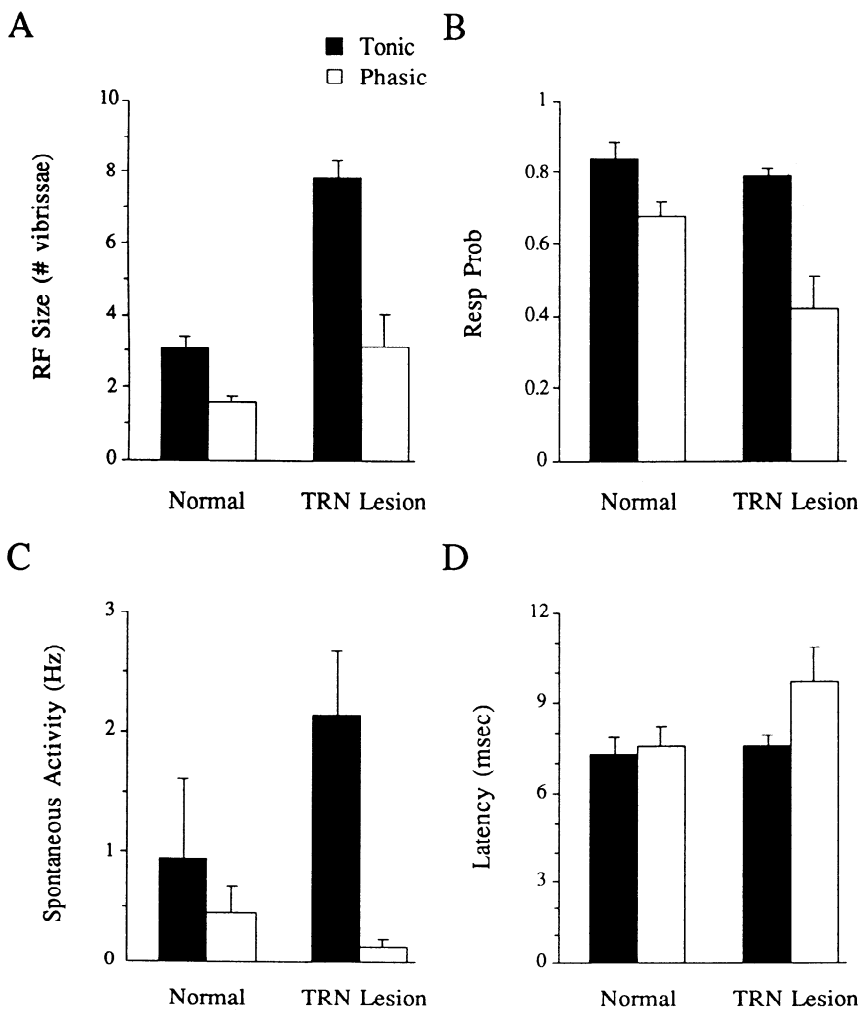

FIG. 10. Comparison of tonically and phasically responding units in terms of (*A*) RF size, (*B*) response probability, (*C*) spontaneous activity, and (*D*) response latency for normal and TRN-lesioned cases (see text for comparison of changes after lesion of TRN). Each bar represents mean ± SE.

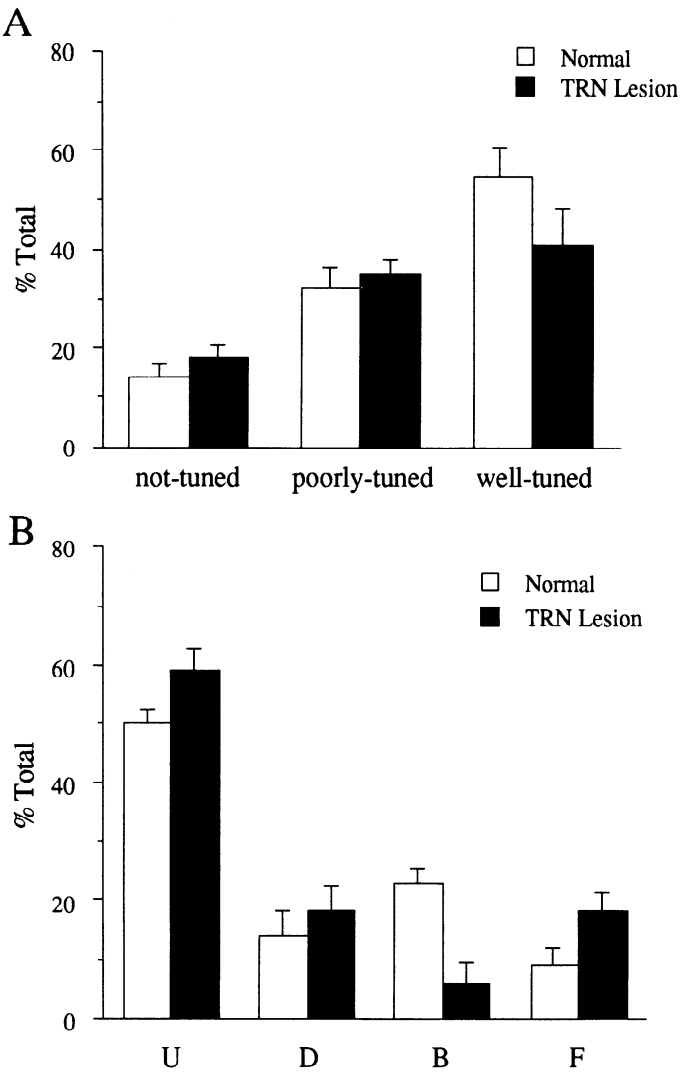

FIG. 11. Proportion of units displaying (*A*) direction selectivity and (*B*) the direction most preferred. The ratio of VPM units lacking directional preference (not tuned) to those tuned to the movement of the whisker in one of four directions, up (U), down (D), backward (B), and forward (F) remained unchanged after the loss of inhibition from TRN. In both normal (n = 102) and TRN-lesioned (n = 97) animals, VPM units clearly responded best to the movement of the whiskers in the up direction.

the vicinity of VP were found that survived the excitotoxic insult. Second, there was a critical volume for a single injection of KA (~100 nl for 2-mM solution) above which the injection inevitably led to a permanent damage to VPM as well as TRN. In such cases, the direct damage to VPM could be predicted by the absence of injury discharge as the electrode was advanced, the spike amplitude when units were encountered being <100 μV and the lack of a clear center RF, all of which were rarely seen in normal or properly lesioned cases. Since the anesthetic state of the animal was monitored at all times, the lack of spontaneous activity and the sluggishness of the response could not be attributed simply to a deeper level of anesthesia. Further, histological analyses after the termination of the experiment clearly correlated these types of responses to VPM cells, which were shrunken or degenerating. Third, the results from iontophoretic studies both from our lab (Lee et al. 1991) and others (Hicks et al. 1986; Salt 1989) have suggested that one of the effects of blocking GABA-mediated inhibition is to increase the proportion of units responding tonically to sensory stimulation. Almost all of the units in our lesioned cases displayed sustained responses. Finally, cells in layers V and VI were carefully analyzed for retrograde degeneration as a result of damage to their axons. Cases included in this study showed no abnormal cell morphologies as a result of retrograde changes or due to direct excitotoxic effects of KA. In addition, corticothalamic neurons in layers V and VI in two long-term survival cases were retrogradely labeled with an injection of horseradish peroxidase in VPM to ensure that inputs from the ipsilateral somatosensory cortex were not disrupted by our lesioning procedure (data not presented here).

VPM function following loss of GABAergic inhibition

An important and consistent observation in this study was an almost immediate increase in the RF size of VPM units mapped after the loss of inhibitory input from TRN. The magnitude of the RF enlargement several hours after the TRN lesion was nearly identical to that seen in VPM after several weeks of survival. The RF size for a typical VPM neuron after the loss of inhibition from TRN was 2–3 times larger than those assessed from control animals.

Recently several reports from this laboratory and others (Friedberg et al. 1989, 1991; Rhoades et al. 1987) have indicated that the number of whiskers that can elicit responses in VPM can be enlarged dramatically by destroying the PrV, which is the primary source of trigeminothalamic input related to vibrissa-sensation (Bruce et al. 1987; Peschanski 1984; Smith 1973). The loss of input from PrV has been shown to enhance the expression of SpVi-mediated responses in VPM (Friedberg et al. 1991; Rhoades et al. 1987). The magnitude of the change after the loss of inhibitory influence from TRN was nearly identical to the one seen after removing PrV (mean RF size = 8.8 vs. 8.4 whiskers, respectively). In this study, the subsequent lesion of SpVi after the loss of TRN resulted in an average RF size that was remarkably similar to the those seen in normal animals (see Table 1).

The other major finding of this study was that the loss of inhibitory drive from TRN alters the nature of evoked responses in VPM to stimulation of the whiskers. In agreement with previous findings (Ito 1988; Simons and Carvell 1989; Sugitani 1990; Waite 1973b), the majority of neurons in VPM displayed very transient responses to prolonged deflections of the whiskers. Indeed, the phasic responses appear to be a characteristic of somatic neurons in the thalamus of cats and monkeys as well as rats (Hicks et al. 1986; Mountcastle et al. 1963). Thus a robust effect of disinhibition in rat VPM was that almost all VPM neurons responded with sustained discharges for the duration of a 50-ms stimulus.

It is interesting to note the features of the response properties in VPM that were not significantly affected by the loss of inhibition arising from TRN. The percentage of neurons selective to movement of whiskers in a particular direction was not altered after the TRN lesion. This finding may be because of the large percentage of neurons already direction selective at the trigeminal level (Nord 1968; Shipley 1974; Waite 1984; Waite and Cragg 1982). Likewise the level of spontaneous activity was not dramatically different when

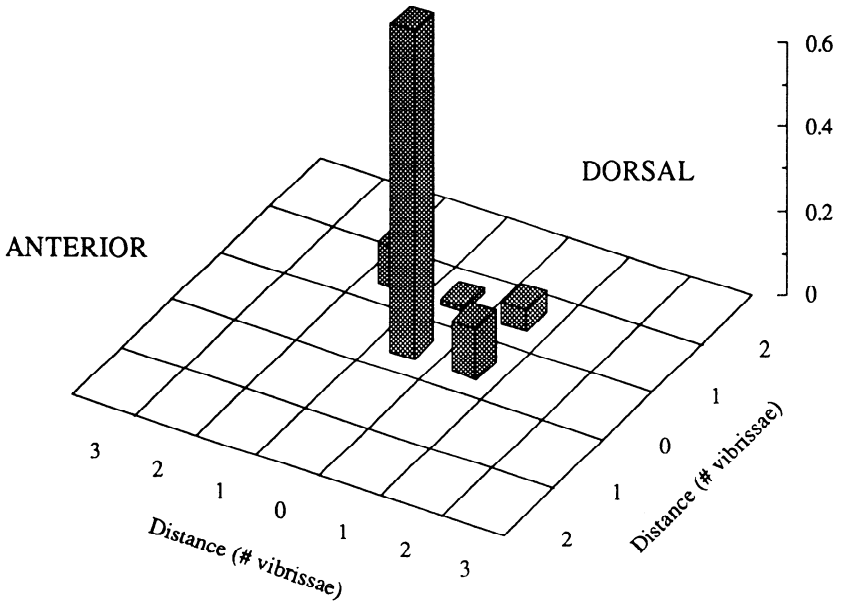

FIG. 12. Average population RF profile similar to Fig. 8 for 7 VPM neurons after a KA lesion of SpVi 30 d after the lesion of TRN. The population profile after such lesions was nearly identical to normal population profiles (compare with Fig. 8*A*).

compared with normal VPM neurons. In addition, GABA-receptor-mediated inhibition in rat VPM does not appear to be responsible for maintaining a strong CRF whisker and a relatively weaker SRF organization. This center-surround relationship appears likely to originate in the brain stem trigeminal nucleus because the rat VPM itself lacks interneurons to construct such an organization through network properties.

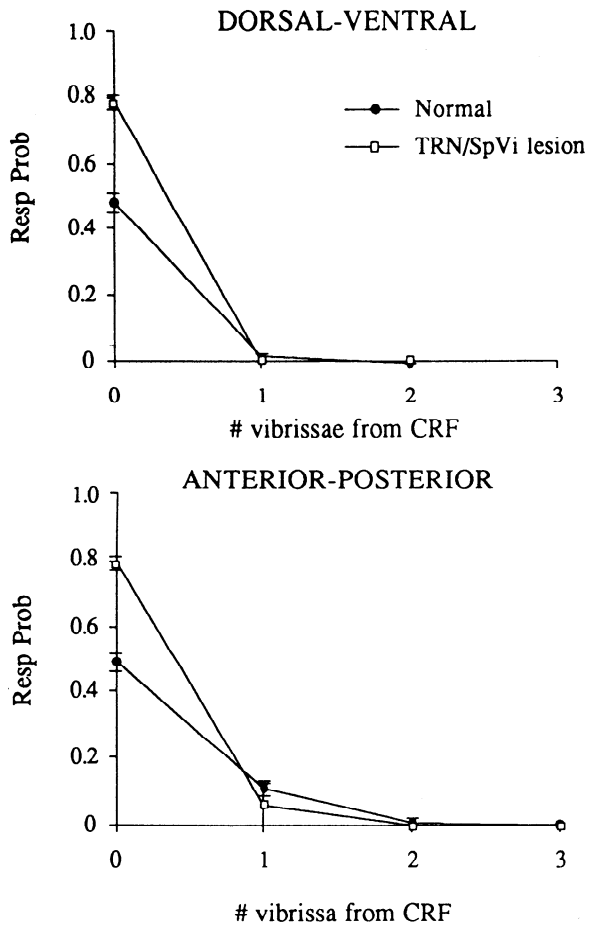

FIG. 13. Plot of the mean response probability for normal and TRN/SpVi-lesioned animals as a function of the number of vibrissae away from the CRF whisker. The SRF values were nearly identical; the average response probability of CRF whiskers in TRN/SpVi-lesioned cases was 67% higher than normal CRF whisker responses ($P < 0.001$, Student's t test). Plots expressed as means ± SE.

We have concluded from these results that in rat VPM, the feedback inhibition from TRN can regulate selectively the expression of the SpVi input. Recent reports by Peschanski and coworkers (1984, 1985) have indicated that projections from PrV and SpVi have completely overlapping distributions. In support of this claim, the acute experiments done in this study showed no overlap in the RF size before and after the TRN lesion (see Fig. 3). We propose that the TRN-inhibition level, which has been reported to be modulated by the ascending activating system (Ben-Ari et al. 1976; Dingledine and Kelly 1977; Jasper 1949; Steriade and Llinás 1988; Steriade et al. 1986), determines the extent to which the trigeminal inputs can functionally converge onto a single VPM neuron. Our data suggests that the magnitude of the evoked response in VPM neurons is determined by the level of GABAergic inhibition in the thalamus rather than by the sensory stimulation of the whiskers in the periphery.

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